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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,085	03/02/2007	Bernard Verrier	033339/305755	9648

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
08/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,085	VERRIER ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. A certified copy of the French priority document, FR0308064, filed 7/2/2003, has been received. Since this priority document is in French, the priority date used for determination of prior art references is the application date for the PCT application, PCT/FR04/01662, filed 6/29/2004.

Information Disclosure Statement

2. The information disclosure statement filed 3/2/2007 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because see notation on IDS, for reference 5. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Drawings

3. The drawings are objected to because the figures in the PCT parent application are labeled in French, no copies with English translation have been provided. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to

the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

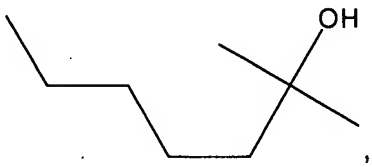
Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claim 2, it is not clear whether the parenthesis is intended to be further limiting or an alternate designation of the subject matter. When an alcohol has the OH

group in the 2-position of a branched n-alkanol, this is not identical to a secondary alcohol. Consider the compound, 2-methylheptan-2-ol: 

, which has an OH group at the 2 position. This C_8 alcohol compound could be considered a branched n-alkanol (n-heptane), with a methyl substituent at the 2 position. However, this compound is not a secondary alcohol, but a tertiary alcohol (where three hydrocarbon substituents are attached to the same C as the OH group). It is not clear whether such compounds are included or excluded from the metes and bounds of the claim.

7. Regarding claim 8 the three concentration designations are not interchangeable. The parts per million units designate the number of particles per total number of particles in a solution, and are consistent with mg/kg and g/kg designations. However ppm is not the same as percent by volume, except when the solvent has a density of 1 mL/mg (about that of water), a condition that is not true for most alcohols or other pharmaceutically acceptable diluents likely to be selected by one skilled in the art. In summary there are many conditions within the metes and bounds of the claim where 0.001-0.1% (v/v) does not correspond to 10-1000 ppm, (nor to 10mg/kg - 1g/kg); therefore the claim is indefinite.

8. Regarding claims 1-2 and 4-8, it is not clear in the case of branched alcohols whether the C_6-C_{10} limitation applies to the n-alkanol chain (the longest linear hydrocarbon part of the molecule) or to the total number of carbons in the molecule. Therefore the claims are indefinite.

9. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "n-alkanol" in claims 1-3, and 5-8 is used by the claim to mean "any linear, branched or cyclic hydrocarbon-chain alcohol", while the accepted meaning is "a linear alcohol." The term is indefinite because the specification does not clearly redefine the term. The phrase "cyclic hydrocarbon-chain", in claims 1 and 3, would not normally be considered a subset of n-alkanols, i.e., cyclic hydrocarbon-chain alcohols are not considered n-alkanols. Therefore, it is not clear which alcohol compounds fall within the metes and bounds of the claims.

10. Claims 1-8 provide for the "use" of C_6-C_{10} hydrocarbon-chain n-alkanols, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activation of CFTR chloride channels by linear 6-10 carbon alcohols with a single OH group in the 1 or 2 carbon position, (i.e., 1-hexanol, 1-heptanol, 1-octanol, 1-nonanol, 1-decanol and 2-octanol) does not reasonably provide enablement for branched, or cyclic alcohols or for alcohols containing more than one OH group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

In one interpretation of the meaning of "use" claims, the claims are drawn to a method of treatment of pathologies related to CFTR chloride channel disorders, such as cystic fibrosis, by using a medicinal product containing a linear, branched or cyclic alcohol a with 6-10 carbon chain. Thus, the claims taken together with the specification imply any linear, branched or cyclic alcohol in the specified size range, with one or more than one (a polyol) OH group is effective in activating CFTR chloride channels, and effective for treating associated diseases, such as cystic fibrosis (CF).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

It is known that about 90% of CF subjects have as at least one allele the deletion of phenylalanine at the 508 position (delF508) of CFTR chloride channel and restoration of chloride permeability in CF is predicted to be of clinical benefit (Verkman, et al.; 2006; Current Pharmaceutical Design; 12, 2235-2247, introduction); various small molecules have been identified that correct the defective gating of these channels and others that correct its defective cellular processing (Verkman, abstract, throughout), although none of these compounds are related to n-alcohols. Two putative mechanisms for the action of n-alcohols in activation of the channel is that octanol binds to a site close to the external surface of CFTR channels or penetrates the membrane to reach a site of action inside the membrane (Marcet et al., British Journal of Pharmacology; 2004; 141, p. 911, last paragraph-p.912, 1st paragraph). Considering the arguments presented by Marcet, the alcohols probably do not bind at the same location as molecules described by Verkman. In testing antiseizure activity of n-alcohols, Likhodi, et al (WO 02/062327 A2; IDS ref 3) have shown that some 2-alcohols, such as 2-pentanol, 2-octanol and 2-

nonanol, are effective in protecting the mice from seizure activity, whereas the compound 1,4-pentanediol (a polyol that contains 2 OH groups) is not active (Table 1).

The art in the area of drug development for such channel defects is unpredictable, in part, because of the complexity of such channels and membranes.

(5) The relative skill of those in the art:

The skill of one in the drug development art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the linear alcohols listed above.

However, the specification does not provide working examples of any branched or cyclic alcohol or of polyols that have activity in activation of CFTR channels.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to alcohols that are bulkier molecules than linear alcohols, such as branched cyclic molecules or alcohols with multiple OH groups and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Applicant has proposed a hydrophobic pocket at the surface of the protein or a site at within the membrane is involved as the active site for activation of the channels by the linear alcohols (specification p.10 & Marcet reference, mentioned above). The steric hinderance that would be introduced by a branched or cyclic alcohol in a pocket of

limited size would result in the inability of the hydroxide group to reach the appropriate location for activation of the chloride channel. Although not related to the CFTR channel, the screening of alcohols disclosed by Likhodi indicates that the diol 1,4-pentanediol does not have activity, while 2-pentanol is active, consistent with the argument that the binding site involved in the mice seizures is subject to such steric hinderance.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-2, and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Llinas et al. (US 4,897,426; IDS Reference 1).

One interpretation of the instant "use" claims is that they are drawn to a medicinal product, which are anticipated by this disclosure. Llinas teaches compositions containing aliphatic alcohols, preferably C3-C10 alkyl alcohols and a physiologically acceptable carrier or diluent (column 5, lines 42-43, 55-58); specifically taught are

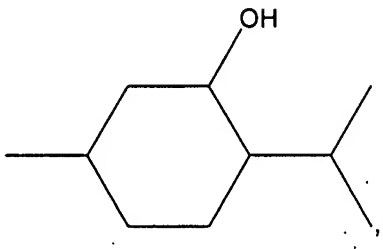
hexanol, heptanol, octanol nonanol and decanol (Table I), most preferred is octyl alcohol (1-octanol; col. 8, line 11); the concentration taught for pentanol is 0.1 and 0.05%, and alcohols with higher molecular weights require lower concentrations, i.e., 10^{-6} M (col 5, lines 12-13; Table I; this corresponds to 130 mg/kg or 130 ppm for octanol). These compositions were intended to inhibit the manifestation of tremor in a mammal (claim 10); however, they would also be useful in treating CFTR chloride channel disorders in humans or animals since the components and concentration ranges are the same. Llinas teaches oral administration in solid or liquid form (i.e., suitable for buccal administration or liquids are suitable for aerosolization or nebulization).

15. Claims 1-2, and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Mak et al. (US 2002/0058650 A1).

Interpreting the "use" claims as product claims, Mak teaches compositions for transdermal application, including aerosols (paragraph 0007), buccal tablets and devices for absorption through mucous membranes (paragraph 0028) that enhance penetration by an alcohol (including the specie octanol (paragraph 0022)) and contain a glycol, such as a dihydric alcohol (paragraph 0024) and oleic acid (a carrier or diluent for the alcohol; abstract).

16. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Delli Santi et al. (US 2002/0081270 A1).

Interpreting the "use" claims as product claims, Delli Santi teaches dental compositions, such as oral rinses, containing 0.01-5 wt % of a phenolic compound, such

as menthol, 

, (a C_{10} cyclic hydrocarbon alcohol) and an orally acceptable carrier (abstract). Such compositions, when provided in liquid form, would be suitable for buccal administration, and would also be suitable for administration in the form of an aerosol or nebulized material. As disclosed by applicant, the same concentration range of the alcohol would be useful in the treatment of CRTR chloride channel disorders, and the diseases listed in instant claim 4. Dell Santi also teaches in some embodiments the inclusion of a polyol, such as sorbitol (a linear C_6 poly alcohol with 6 OH groups) (claim 8); which would also have the activity disclosed by applicant.

17. Claims 1-2, and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Likhodi, et al (WO 02/062327 A2; IDS Ref 3).

This rejection is applicable to the interpretation of the "use" claims as drawn to a product. Likhodi teaches pharmaceutical compositions comprised of an alcohol and a pharmaceutically acceptable carrier or diluent (p. 9, lines 16-19); specific alcohols taught include 2-nonanol and 2-octanol (p. 15, lines 3-4); forms taught include those appropriate for buccal or nasal administration (p. 16, line 22); nasal administration can be in the form of aerosols and pump-atomizer (nebulizer) in an aqueous or non-aqueuos solvent (p. 17, lines 22-p. 18, line 2).

18. Claims 1-2 and 4-6 and 8 are rejected under 35 U.S.C. 102 (a) & (e) as being anticipated by Marcet et al. (British Journal of Pharmacology; 2004; 141, 905-914)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The "use" claims may also be interpreted as drawn to a method of treating pathology related to CFTR chloride channel disorders in humans or animals, toward which the rejection is based. Marcet teaches 1-heptanol, 1-octanol, 2-octanol and 1-decanol activate CFTR chloride channels in human and hamster cells and suggests that these compounds may be used for therapeutic strategies of CF (abstract); concentrations taught cover the range from 0.1-10 mM, or 0.001-0.1% (v/v) (p. 906, methods, first paragraph); aerosol administration by inhalation is taught (p. 912, 2nd column).

19. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Conclusion

20. All claims are rejected.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571)

272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TPT/
Timothy P. Thomas
Patent Examiner

Ardin H Marschel 8/16/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER